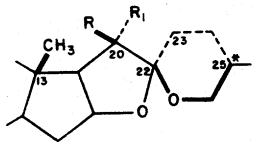
## STEROIDAL SAPOGENINS. XX. CONFIGURATION OF SPIROKETAL SIDE CHAIN AT CARBON 22[1]

*Sir:*

In a recent communication Scheer, Kostic and Mosettig[2] state that Sa[3] and Sm are not isomeric at both $C_{22}$ and $C_{25}$ as previously believed[4] but differ only at $C_{25}$. We feel this view is incorrect. Not only is there excellent evidence available to show that Sa and Sm are isomeric at $C_{22}$, but in view of the establishment of the configuration of steroidal sapogenins at $C_{20}$[1] it is now possible for the first time to designate the actual configuration of Sa and Sm at $C_{22}$.

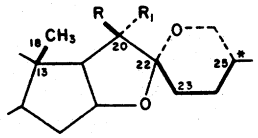
The evidence that Sa and Sm are isomeric at $C_{22}$ is convincing: (a) Sa and Sm have different infrared spectra in the region 850–1350 K.[5,6] These are believed to be due to the vibrations of the –C–O–C–O–C– spiroketal system constrained by the two E and F rings. When this system is disrupted, as in formation of dihydrosapogenins, these characteristic bands disappear.[5,6] As we have shown previously,[1] Sa and Sm are identical at $C_{20}$ and isomerism at $C_{25}$ has no effect on infrared spectra. Therefore the spectral differences between Sa and Sm must be due to isomerism at $C_{22}$. (b) Prolonged refluxing of 22b-spirostanes, such as Sa or its dihydroxy analog, with alcoholic hydrochloric acid converts them to the isomeric 22a series.[4,7,8] This can be possible only if Sa and Sm were isomeric at $C_{22}$. (c) Djerassi, Martinez, and Rosenkranz[9] have shown that Sa under proper conditions forms a *23-dibromide* whereas Sm and other 22a-spirostanes form only *23-monobromides*. We have confirmed this. Again this difference is possible only if Sa and Sm are *isomeric* at $C_{22}$.

The bromination data in conjunction with the established configuration at $C_{20}$[1] permits, for the first time, assignment of configuration at $C_{22}$. Molecular models corresponding to IA and IIA in Fig. 1 were constructed. On account of the hindrance of the methyl group attached to $C_{20}$ it is impossible to construct a 23-dibromide of IA. Therefore it is Sm. A 23-dibromide can easily be constructed from IIA. Therefore it is Sa. By analogy we assign configurations IB and IIB to 20-iSm and 20-iSa, respectively.[1] In this case 20-iSm should form a dibromide and experiments to confirm this will be reported at a later date.



I-A Smilagenin
R = H, $R_1$ = $CH_3$

I-B 20-Isosmilagenin
R = $CH_3$, $R_1$ = H



II-A Sarsasapogenin
R = H, $R_1$ = $CH_3$

II-B 20-Isosarsasapogenin
R = $CH_3$, $R_1$ = H

Fig. 1.—Configurations of sarsasapogenin and smilagenin and their 20-isoanalogs at carbons 20 and 22.

Scheer, Kostic and Mosettig[2] converted Sa and Sm to identical 16,22-epoxycoprostan-3$\beta$-ol derivatives via catalytic hydrogenation, selective tosylation at $C_{26}$, followed by $LiAlH_4$ reduction. Using a somewhat modified procedure involving catalytic hydrogenation of the 3-acetates, tosylation at $C_{26}$, replacement of tosyl with iodine, followed by zinc–acetic acid reduction, hydrolysis, and formation of the nicely crystalline 3-3,5-dinitrobenzoates, we confirmed these workers' findings: 16,22-epoxycoprostan-3$\beta$-ol-3[3,5-dinitrobenzoate, m.p. 236–237°, $[\alpha]_D^{25}$ +6.2°. Calculated for $C_{34}H_{48}N_2O_7$: C, 68.51; H, 8.12. Found: C, 68.38; H, 8.20].

This, however, *does not prove* that Sa and Sm are identical at $C_{22}$. This would be true only if DSa and DSm retain configuration at $C_{22}$ during hydrogenation. We wish to present evidence that during catalytic hydrogenation the configuration of DSm at $C_{22}$ probably is changed from that of Sm and becomes identical to that of DSa, whereas DSa does not change configuration.

On catalytic hydrogenation 20-iSa and 20-iSm give dihydro derivatives D20-iSa and D20-iSm identical to those obtained from similar hydrogenation of PSa and PSm diacetates.[1] Therefore, the location of the hydrogen atom at $C_{20}$ in dihydropseudosapogenins is known, *i.e.*, it is identical to that of 20-isosapogenins as in IB and IIB.[10] Since catalytic hydrogenation of an olefinic bond usually results in a *cis* configuration,[11] we assign formulations IIIA and IIIB, Fig. 2, to D20-iSm = PDSm and D20iSa = PDSa. Entrance of the hydrogen atoms on the rear faces of $C_{20}$ and $C_{22}$ is in complete accord with the structures of PSa and PSm in which the front faces of $C_{20}$-$C_{22}$ are almost completely shielded by methyl groups attached to $C_{18}$ and $C_{20}$.

(1) Paper XIX. M. E. Wall, C. R. Eddy and S. Serota, THIS JOURNAL, **76**, 2849 (1954).

(2) I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **75**, 4871 (1953).

(3) Abbreviations used in this paper: Sa = sarsasapogenin, Sm = similagenin, P = pseudo, D = dihydro, 20-i = 20-iso. Thus D20-iSa = dihydro 20-isosarsasapogenin.

(4) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 846 (1939).

(5) M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

(6) R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **76**, 158 (1953).

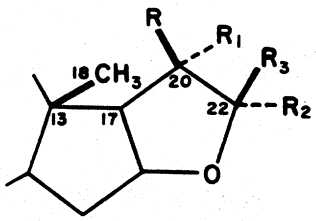
(7) M. E. Wall, C. R. Eddy, S. Serota and R. F. Mininger, *ibid.*, **75**, 4437 (1953).

(8) We have confirmed Marker's findings in regard to the conversion of Sa to Sm[4] and have found the spectral differences associated with 22b- and 22a-spirostanes[5,6]

(9) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951).

(10) Hydrogenation of sapogenins does not affect the configuration at $C_{22}$. For example Sa, which is stable to $CrO_3$ oxidation, hydrogenates to DSa likewise stable, 20 iSa unstable to $CrO_3$ oxidation, hydrogenates to D20-iSa which is equally unstable.

(11) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed. John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 297–298.




IIIA, $D_{20}$iSm = DPSm, R = $CH_3$, $R_1 = R_2 = H$, $R_3 =$

$$-(CH_2)_2-\underset{\underset{CH_3}{|}}{\overset{\overset{H}{|}}{C}}-CH_2OH$$

IIIB, $D_{20}$iSa = DPSa, R = $CH_3$, $R_1 = R_2 = H$, $R_3 =$

$$-(CH_2)_2-\underset{\underset{H}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2OH$$

IVA, DSm, $R_1 = CH_3$, $R = R_2 = H$, $R_3 =$

$$-(CH_2)_2-\underset{\underset{CH_3}{|}}{\overset{\overset{H}{|}}{C}}-CH_2OH$$

IVB, DSa, $R_1 = CH_3$, $R = R_2 = H$, $R_3 =$

$$-(CH_2)_2-\underset{\underset{H}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2OH$$

Fig. 2.—Configuration of dihydro and dihydro 20-iso-analogs of sarsasapogenin and smilagenin.

From a consideration of the formulations in Figs. 1 and 2, it is seen that catalytic hydrogenation of 20-iSm (IB) to form D20-iSm (IIIA) involves a *change* in $C_{22}$ configuration to that identical with D20-iSa (IIIB). Formation of IIIB from 20-iSa (IIB) does not involve a change in $C_{22}$ configuration. Hence D20-iSm and D20-iSa are now isomeric only at $C_{25}$. It is most probable that hydrogenation of Sm (IA) and Sa (IIA) to DSm (IVA) and DSa (IVB), respectively, involves a similar mechanism. Accordingly, the formation of the same 16,22-epoxy-coprostan-3$\beta$-ol from Sm and Sa *is not incompatible* with $C_{22}$ isomerism of these sapogenins.